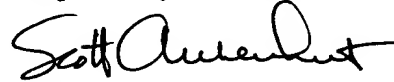


The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

Attached hereto is a marked-up version of the changes made to the Specification by the current Amendment. The attached pages are captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the Specification:**

Paragraph beginning at line 14 of page 21 has been amended as follows:

PDZ domains of proteins are named after three prototypical proteins: PSD95, Drosophila large disc protein and Zonula Occludin 1 protein (Gomperts et al., 1996, *Cell* 84:659-662). PDZ domain-containing proteins are involved in synapse formation by organizing transmembrane neurotransmitter receptors through intracellular interactions. PDZ domains contain the signature sequence GLGF (SEQ ID NO:29). In the nervous system, typical PDZ domain-containing proteins contain three PDZ domains, one SH3 domain and one guanylate kinase domain. Examples of intracellular PDZ domain-containing proteins include LIN-2, LIN-7 and LIN-10 at the pre-synapse, and PSD95 at the post-synapse.

Paragraph (TABLE 2) beginning at line 1 of page 26 has been amended as follows (see attached sheets).

Paragraph (TABLE 3) beginning at line 1 of page 33 has been amended as follows (see attached sheets).

Paragraph beginning at line 25 of page 50 has been amended as follows:

As noted *supra*, PCR primers were designed to include endonuclease restriction sites to facilitate ligation of PCR fragments into a GST gene fusion vector (pGEX-3X; Pharmacia, GenBank accession no. XXU13852) in-frame with the glutathione-S transferase coding sequence. This vector contains a IPTG inducible lacZ promoter. The pGEX-3X vector was linearized using *Bam* HI and *Eco* RI or, in some cases, *Eco* RI or *Sma* I, as shown in **TABLE 3**, and dephosphorylated. For most cloning approaches, double digest with *Bam* HI and *Eco* RI was performed, so that the ends of the PCR fragments to clone were *Bam* HI and *Eco* RI. In some cases, restriction endonuclease combinations used were *Bgl* II

# PDZ-LIGAND/PDZ INTERACTION SUMMARY

TABLE 2

| PDZ LIGAND            | CODE    | SEQ   | SEQ<br>ID<br>NO. | CASK | MPP1 | DLG1 | PSD95 | NeDLG | TAX33 | SYN1a | TAX 43 | LDP | LIM | LIMK1 | LIMK2 | MPP2 |
|-----------------------|---------|-------|------------------|------|------|------|-------|-------|-------|-------|--------|-----|-----|-------|-------|------|
| CD6                   | AA6L    | ISAA  | 14               |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CD49E (alpha-4)       | AA11L   | TSDA  | 24               |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CD49F (Aform. alpha6) | AA12L   | TSDA  | 24               |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CD166 (CD6L)          | AA20L   | KTEA  | 64               |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CD148                 | AA55L   | KTIA  | 278              |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CC CKR-2              | AA42L   | KEGA  | 283              |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CD138 (syndecan)      | AA18L   | EFYA  | 89               | *    |      |      |       |       |       |       |        |     |     |       |       |      |
| CD148 (DEP-1)         | AA19L   | GYIA  | 119              |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CD98 (2F4)            | AA15L   | PYAA  | 54               |      |      |      |       |       |       |       |        |     |     |       |       | G    |
| CLASP-1               | AA1L    | SAEV  | 284              |      |      | G    | A     | G     |       |       |        |     |     |       |       |      |
| CLASP-4               | AA3L-V  | YAEV  | 228              |      |      | A    | A     | A     |       |       |        | A   |     |       |       |      |
| NMDA                  | AA34.2L | ESDV  | 263              |      | A    | A/G  | A/G   | A/G   |       | G     | A      |     |     | A     |       | G    |
| VCAM1                 | AA17L   | KSKV  | 163              |      | A    | A    |       | A     |       |       |        | A   |     |       |       |      |
| CLASP-2               | AA2L    | SSVV  | 223              |      |      | A/G  | A/G   | A/G   |       |       |        |     |     |       |       |      |
| CD95 (Apo-1/Fas)      | AA13L   | QSLV  | 44               |      |      | A/G  | A/G   | A/G   |       |       |        |     |     |       |       |      |
| KV1.3                 | AA33L   | FTDV  | 238              |      |      | A/G* | A/G*  | A/G   |       |       |        |     |     | A     |       |      |
| DNAM-1                | AA22L   | KTRV  | 74               |      | A    | A    | A/G   | A     |       |       |        |     | A   |       |       | G    |
| CD83                  | AA47L   | TELV  | 248              |      |      | A    | A     | A     |       |       |        |     |     |       |       |      |
| CD44 (long form)      | AA9L    | KIGV  | 104              |      | G    |      |       |       |       |       |        |     |     |       |       |      |
| Neurexin              | AA38L   | EYYV  | 268              | G*   | A*   | A/G  | A/G   | G     |       | A     | A      |     |     | A     |       |      |
| CD97 (CD55L)          | AA14L   | ESGI  | 49               |      |      | A    |       |       |       |       |        |     |     |       |       |      |
| Glycophorin C         | AA37L   | EYFI  | 273              |      | *    | G    | G     | G     |       |       |        |     |     |       |       | A    |
| CDW128A (IL8RA)       | AA29.1L | SSNL  | 69               |      |      | A    |       | A     |       |       |        |     |     |       |       |      |
| CD3n                  | AA4L    | SSQL  | 4                |      |      | A    | A     |       |       |       |        |     |     |       |       |      |
| LPAP                  | AA30L   | VTAL  | 84               |      |      | A    |       |       |       |       |        |     |     |       |       |      |
| CD46 (form 1)         | AA10L   | FTSL  | 109              |      |      | A/G  | A/G   | G     |       |       |        |     |     |       |       |      |
| CDW128B (IL8RB)       | AA29.2L | STTL  | 233              |      |      | A/G  | A     | A/G   |       |       |        |     |     |       |       |      |
| DOCK2                 | AA40L   | STD L | 243              |      |      | A    | A/G   | G     |       | G     |        |     |     |       |       |      |
| CD34                  | AA7L    | DTEL  | 149              |      |      | A    | A     | G     |       |       |        |     |     |       |       |      |
| CD5                   | AA49L   | AQRL  | 285              |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CC CKR-4              | AA44L   | HDAL  | 286              |      |      |      |       |       |       |       |        |     |     |       |       |      |
| FceRib                | AA25L   | PIDL  | 129              |      |      |      |       |       |       |       |        |     |     |       |       |      |
| FasLigand             | AA23L-M | LYKL  | 79               |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CD62E                 | AA48L   | SYIL  | 168              |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CC CKR-1R             | AA41L   | SAGF  | 287              |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CDW125 (IL5R)         | AA28L   | DSVF  | 94               |      |      |      |       |       |       |       |        |     |     |       |       |      |
| BLR-1                 | AA45L   | LTTF  | 253              |      |      |      |       |       |       |       |        |     |     |       |       |      |
| CC CKR-3              | AA43L   | SIVF  | 288              |      |      |      |       |       |       |       |        |     |     |       |       |      |
|                       |         |       |                  | CASK | MPP1 | DLG1 | PSD95 | NeDLG | TX33  | SYN1a | TX 43  | LDP | LIM | LIMK  | LIMK2 | MPP2 |

\* Interactions described in the scientific literature

# PDZ-LIGAND/PDZ INTERACTION SUMMARY

TABLE 2  
CONTINUED

| NOS1 | AF6 | PTN-4 | prIL16 | 41.8 | K559 | RGS12 | K316 | DVL1 | TAX 40 | TIAM1 | MINT1 | K303 | CBP | MINT3 | TAX 2 | K561 | PDZ LIGAND            |
|------|-----|-------|--------|------|------|-------|------|------|--------|-------|-------|------|-----|-------|-------|------|-----------------------|
|      |     |       |        | A    |      |       |      |      |        |       |       |      |     |       |       |      | CD6                   |
|      |     |       |        | A/G  |      |       |      |      |        |       |       |      |     |       |       |      | CD49E (alpha-4)       |
|      |     |       |        | A/G  |      |       |      |      |        |       |       |      |     |       |       |      | CD49F (Aform, alpha6) |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CD166 (CD6L)          |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CD148                 |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CC CKR-2              |
|      |     |       |        | A/G  |      |       |      |      |        | A     |       |      |     |       |       |      | CD138 (syndecan)      |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CD148 (DEP-1)         |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CD98 (2F4)            |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CLASP-1               |
|      | A   |       |        | A    |      |       |      |      |        |       | A     |      |     |       |       |      | CLASP-4               |
|      |     | A/G   |        | A/G  |      | A/G   |      | A    |        |       | A/G   |      |     |       | A     | G    | NMDA                  |
|      |     |       |        | A    |      |       |      |      |        | A     |       | A    |     |       |       |      | VCAM1                 |
|      |     |       |        | A    |      |       |      |      |        |       |       |      |     |       |       |      | CLASP-2               |
|      |     |       |        | A/G  |      |       |      |      |        |       |       |      |     |       |       |      | CD95 (Apo-1/Fas)      |
|      |     |       |        | A    |      | A     |      | A    |        |       | G     |      |     |       |       |      | KV1.3                 |
|      | A   |       |        | A    |      | A     |      |      |        |       |       |      |     |       |       |      | DNAM-1                |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CD83                  |
|      |     |       | G      |      |      |       |      |      |        |       | G     |      |     |       |       |      | CD44 (long form)      |
|      | A   |       | A      | A    |      | A     |      | A    | A      | A     | A/G   |      |     |       |       |      | Neurexin              |
|      |     |       |        | A    |      |       |      |      |        |       |       |      |     |       |       |      | CD97 (CD55L)          |
|      | A   |       |        | A    |      |       |      |      |        |       | A     |      |     |       |       |      | Glycophorin C         |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CDW128A (IL8RA)       |
|      |     |       |        | A/G  |      |       |      |      |        |       | A/G   |      |     |       |       |      | CD3n                  |
|      |     |       |        |      |      |       |      |      |        |       | G     |      |     |       |       |      | LPAP                  |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CD46 (form 1)         |
|      |     |       |        | A    |      | *     |      |      |        |       |       |      |     |       |       |      | CDW128B (IL8RB)       |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       | G    | DOCK2                 |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CD34                  |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CD5                   |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CC CKR-4              |
|      |     |       |        |      |      |       |      |      |        |       | A     |      |     |       |       |      | FceRib                |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       | G    | FasLigand             |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CD62E                 |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CC CKR-1R             |
|      |     | G     |        |      |      | G     |      |      |        |       |       |      |     |       |       |      | CDW125 (IL5R)         |
|      |     |       |        |      |      |       |      |      |        |       | G     |      |     |       |       |      | BLR-1                 |
|      |     |       |        |      |      |       |      |      |        |       |       |      |     |       |       |      | CC CKR-3              |
| NOS1 | AF6 | PTN-4 | prIL16 | 41.8 | K559 | RSG12 | K316 | DVL1 | TX 40  | TIAM1 | MINT1 | K303 | CBP | MINT3 | TX 2  | K561 |                       |

\* Interactions described in the scientific literature

TABLE 3  
PDZ DOMAINS

Key:

Gene names and corresponding gene products are provided. In some cases, cDNA sequences representing the same gene have several database entries under different accession numbers and names. Accession numbers shown correspond to the gene name used in this description, and numbering of nucleotides and amino acids correlates to those Genbank entries. Amino acid sequences shown correspond to the cloned DNA portions of PDZ domain containing genes. Linker amino acid sequences (e.g., amino acids encoded by DNA flanking the cloning site of the pGEX-3X cloning vector) are in italics

| GENE SYMBOL | PROTEIN | ACC. # | AMINO ACID SEQUENCE*   | CLON. SITES        | FORWARD PRIMER   | REVERSE PRIMER  |
|-------------|---------|--------|--|--------------------|--|---|
| CASK        | CASK    | Y17138 | AA495-584;<br>PDZ domain 1 (of 1)  | Bam HI /<br>Eco RI | 6CAF<br>5' -<br>TCGGATCCAT<br>GTGACCAGAG<br>TTCGG-3'<br>(SEQ ID<br>NO:322) | 7CAR<br>5' -<br>TCGGAATTCAG<br>ACTGAGTGCGG<br>TA-3'<br>(SEQ ID<br>NO:323) |
|             |         |        | HVTRVRLVQFQKNTDEPMGITLK<br>MNELNHCIVARIMHGGMIHRQGT<br>LHVGDEIREINGISVANQTVEQL<br>QKMLREMRGSITFKIVPSYRTQS<br>LNSS (SEQ ID NO:292) |                    | N1471-1494   | N1761-1738  |

|      |   |        |  |                    |   |  |
|------|---|--------|--|--------------------|---|--|
| MPP1 | 55 Kd<br>erythrocyte<br>membrane<br>protein | M64925 | AA101-186;<br>PDZ domain 1 (of 1)<br><br>RKVRLIQFEKVTPEPMGITLKLN<br>EKQSCTVARILHGGMIHRQGS<br>VGDEILEINGTNTNHSVDQLQK<br>AMKETGMISLKVIPNQREFIVT<br>D (SEQ ID NO:293) | Bam HI /<br>Bam HI | 62MPF<br><br>5' -<br>GGGATCCGGA<br>AAGTGGGACT<br>CATAC-3'<br>(SEQ ID<br>NO:324) | 63MPR<br><br>5' -<br>ACGGATCCGCT<br>GGTTGGGAATT<br>ACTT-3'<br>(SEQ ID<br>NO:325) |
|      |   |        |  |                    | N296-320  | N568-543   |

|      |   |        |  |                    |  |  |
|------|---|--------|--|--------------------|--|--|
| DLG1 | human<br>homolog of<br>Drosophila<br>discs large<br>protein | U13897 | AA275-477;<br>PDZ domains 1-2 (of 3)<br><br>QVNGTDADYEYEEITLERGNSGL<br>GFSIAGGTDNPHIGDDSSIFITK<br>IITGGAAAQDGRRLRVNDCILQVN<br>EVDVRDVTHSKAVEALKEAGSIV<br>RLYVKKRRKPVSEKIMEIKLIKGP<br>KGLGFSIAGGVGNQHIPGDNISY<br>VTKIIEGGAHKGDKLQIGDKLL<br>AVNNVCLLEEVTHEEAVTALKNTS<br>DFVYLKVKAPTSMYMNDGYAPNS<br>S (SEQ ID NO:294) | Bam HI /<br>Eco RI | 1DF<br><br>5' -<br>TCGGATCCAG<br>GTTAATGGCT<br>CAGATG-3'<br>(SEQ ID<br>NO:326) | 2DR<br><br>5' -<br>CGGAATTCGGT<br>GCATAGCCATC<br>-3'<br>(SEQ ID<br>NO:327) |
|      |   |        |  |                    | N815-841   | N1442-1421   |

|       |  |        |  |                    |  |   |
|-------|--|--------|--|--------------------|--|---|
| PSD95 | human post-synaptic density protein 95 | U83192 | AA387-724;<br>PDZ domains 1-3 (of 3)<br><br>LEEGEMEYEEITLERGNSGLGF<br>SIAGGTDNPHIGDDPSIFITKII<br>PGGAAQDGRRLRVNDSILFVNEV<br>DVREVTHTSAAVEALKEAGSIVRL<br>YVMRRKPPAEKVMEIKLIKGPKG<br>LGFSIAGGVGNQHIPGDNSIYVT<br>KIIEGGAHKGRLQIGDKILAV<br>NSVGLEDVMHEDAVAALKNTYDV<br>VYLKVAKPSNAYLSDSYAPPDIT<br>TSYSQHLDNEISHSSYLGTDYPT<br>AMTPTSPRRYSPVAKDLLGEEDI<br>PREPRRIVIHrgSTGLGFNIVGG<br>EDGEGIFISFILAGGPADLSGEL<br>RKGDQILSVNGVDLNRNASHEQAA<br>IALKNAGQTVTIIAQYKPEFIV<br>(SEQ ID NO:295) | Bam HI /<br>Eco RI | 8PSF<br>5'-<br>TCGGATCCTT<br>GAGGGGAGA<br>TGA-3'<br>(SEQ ID<br>NO:328) | 11PSR<br>5'-<br>TCGGAATTGCG<br>TATACTCTTCT<br>GG-3'<br>(SEQ ID<br>NO:329)<br><br>N2191-2168 |
|-------|--|--------|--|--------------------|--|---|

|       |   |          |  |                    |   |   |
|-------|---|----------|--|--------------------|---|---|
| NeDLG | presynaptic protein<br>saol02<br>(neuroendocrine-dlg) | U49089   | AA205-1171;<br>PDZ domains 1-2 (of 3)<br><br>QYEEIVLERNGLGFSIAGGID<br>NPHVPDDPGIFITKIIPGAAAM<br>DGRLGVNDCVLRVNEVEVSEVH<br>SRAVEALKEAGPVVRLVVRRRQP<br>PPETIMEVNLLKGPGLGFSIAG<br>GIGNQHIPGDNISIYITKII EGGA<br>AQKDGRLLQIGDRLLAVNNTNLQD<br>VRHEEAVASLKNSTSDMVYLKVAK<br>PGSPR ( <u>SEQ ID NO:296</u> ) | Bam HI /<br>Eco RI | 71NEDF<br><br>5' -<br>CAGGATCCAA<br>TATGAGGAAA<br>TCGTACTTG-<br>3' ( <u>SEQ ID NO:330</u> )<br><br>N608-635 | 72NEDR<br><br>5' -<br>TTGAATTTCGAG<br>GCTGCCTGGCT<br>TGGC-3' ( <u>SEQ ID NO:331</u> )<br><br>N1186-1161 |
| TAX33 | tax interaction protein 33                            | AF028826 | AA73-162;<br>PDZ domain 1 (of 1)<br><br>HSHPRVVELPKTDEGLGFNVMMG<br>KEQNSPIYISRIIPGGVAERHGG<br>LKRGDQLLSVNGVSVEGEHHEKA<br>VELLKAADKDSVKLVVRYTPKVL E<br>FIVTN ( <u>SEQ ID NO:297</u> )   | Bam HI /<br>Eco RI | 92TAF<br><br>5' -<br>GTGGATCCA<br>CTCCCACCCT<br>CGAGTAG-3' ( <u>SEQ ID NO:332</u> )<br><br>N208-234         | 93TAR<br><br>5' -<br>CATGAATTCCA<br>GAACCTTTGGG<br>TGTATCGC-3' ( <u>SEQ ID NO:333</u> )<br><br>N497-468 |



|                |                   |        |   |                    |  |   |
|----------------|-------------------|--------|---|--------------------|--|---|
| SYN 1 $\alpha$ | alpha1-syntrophin | U40571 | AA96-189<br>PDZ domain 1 (of 1)<br>QRRRTVVRKADAGGLGISIKGGR<br>ENKMPILISKIFKGLAADQTAL<br>FVGDAILSVNGEDLSSATHDEAV<br>QVLKKTGKEVVLEVKYMKDVSPI<br>FKNSS (SEQ ID NO:298) | Bam HI /<br>Eco RI | 124SYF<br>5' -<br>TACGGATCCA<br>GCGCCGCCG<br>CGTGAC-3'<br>(SEQ ID<br>NO:334) | 125SYR<br>5' -<br>GTAGAATTCTT<br>GAAATACGGTG<br>AGAC-3'<br>(SEQ ID<br>NO:335) |
|                |                   |        |   |                    | N279-301   | N576-551  |

|       |  |          |  |                    |   |   |
|-------|--|----------|--|--------------------|---|---|
| TAX43 | human tax<br>interaction<br>protein 43 | AF028828 | AA15-85<br>PDZ domain 1 (of 1)<br>QKRGVKVLKQELGGLGISIKGGK<br>ENKMPILISKIFKGLAADQTAL<br>YVGDAILSVNGADLRDATHDEAV<br>QALQFIVTN (SEQ ID<br>NO:299) | Bam HI /<br>Eco RI | 97TAF<br>5' -<br>TCTGGATCCA<br>GAAGCGTGGC<br>GTGAAGG-3'<br>(SEQ ID<br>NO:336) | 98TAR<br>5' -<br>CGGAATTCAAC<br>GCCTGCACCGC<br>CTC-3'<br>(SEQ ID<br>NO:337) |
|       |  |          |  |                    | N37-63  | N267-231  |

|     |                           |        |  |                    |  |  |
|-----|---------------------------|--------|--|--------------------|--|--|
| LDP | lim domain protein clp-36 | U90878 | AA46-88<br>PDZ domain 1 (of 1)<br><br>RGMTTQQIDLQGPWPWFRLVGR<br>KDFEQPLAISRVTPGSKAALASS<br>(SEQ ID NO:300) | Bam HI /<br>Eco RI | 146LIF<br>5' -<br>CCAGGATCCG<br>CGGAATGACC<br>ACCCAGC-3'<br>(SEQ ID<br>NO:338) | 147LIR<br>5' -<br>CATGAATTCCG<br>TAGAGCCGCCT<br>TGCTT-3'<br>(SEQ ID<br>NO:339) |
|     |                           |        |  |                    | N129-155   | N276-239   |

|       |                           |           |  |                    |  |  |
|-------|---------------------------|-----------|--|--------------------|--|--|
| LIM   | Human LIM protein         | AF061258  | AA29-112;<br>PDZ domain 1 (of 1)<br><br>LSNYSVSLVGPAPWGFRLQGGKD<br>FNMPLTISSLKDGKAAQANVRI<br>GDVVLSDIGINAQGMTHLEAQNK<br>IKGCTGSLNMTLQRASC (SEQ<br>ID NO:301)                       | Bam HI /<br>Eco RI | 182LF<br>5' -<br>TTAGGATCCT<br>GAGCAAGTAC<br>AGTGTGTAC<br>-3'<br>(SEQ ID<br>NO:340)<br>N86-115 | 183LR<br>5' -<br>CTTGAATTACAG<br>CAGATGCTCTT<br>TGCAGAGTC-<br>3'<br>(SEQ ID<br>NO:341)<br>N350-320 |
| LIMK1 | human LIM domain kinase 1 | NM_002314 | AA194-291;<br>PDZ domain 1 (of 1)<br><br>TVTLVSI PASSHGKRLSVSIDP<br>PHGPPGCGTEHSHTVRVQGVDPG<br>CMSPDVKNSIHVGDRILEINGTP<br>IRNVPLDEIDLLIQETSRLLQLT<br>LEHDPGIHRD (SEQ ID<br>NO:302) | SMA I              | 52LIFP<br>5' -<br>CTGCCCGGGA<br>CCGTACCCCT<br>GGTGTC-3'<br>(SEQ ID<br>NO:342)<br>N570-597      | 53LIRP<br>5' -<br>TCGCCCGGTC<br>ATGCTCGAGGG<br>TC-3'<br>(SEQ ID<br>NO:343)<br>N874-851             |

|       |                           |        |  |                    |  |   |
|-------|---------------------------|--------|--|--------------------|--|---|
| LIMK2 | human LIM domain kinase 2 | D45906 | AA185-275;<br>PDZ domain 1 (of 1)<br><br>PYSVTLISMPATTEGRRGFVS<br>ESACSNYATTVOQKEVNRMHIS<br>NNRNAIHPGDRILEINGTPVRTL<br>RVEEVEDAISQTSQTLQLLIEHE<br>FIVTN ( <u>SEQ ID NO:303</u> ) | Bam HI /<br>Eco RI | 185LF<br><br>5' -<br>AGCGGATCCC<br>CTACTCTGTC<br>ACGCTCATC-<br>3' ( <u>SEQ ID NO:344</u> )<br><br>N545-573 | 186LR<br><br>5' -<br>GACGAATTCAT<br>GTTCAATCAAC<br>AGCTGAAG-3' ( <u>SEQ ID NO:345</u> )<br><br>N834-805 |
|-------|---------------------------|--------|--|--------------------|--|---|

|      |                                     |        |  |                    |   |   |
|------|-------------------------------------|--------|--|--------------------|---|---|
| MPP2 | maguk p55 subfamily member 2 (DLG2) | X82895 | AA185-273;<br>PDZ domain 1 (of 1)<br><br>QPVPPDAVRMVGIRKTAGEHLGV<br>TFRVEGGELVIARILHGGMVAQQ<br>GLLHVGDIIKEVNGQPVGSDPRA<br>LQELLRNASGSVILKILPNYQVF<br>IVTD ( <u>SEQ ID NO:304</u> ) | Bam HI /<br>Eco RI | 142MF<br><br>5' -<br>TCAGGATCCA<br>GCCTGTACCT<br>CCCGATGC-<br>3' ( <u>SEQ ID NO:346</u> )<br><br>N542-569 | 143MR<br><br>5' -<br>ATGGAATTCCT<br>GGTAGTTGGGC<br>AGGATC-3' ( <u>SEQ ID NO:347</u> )<br><br>N828-801 |
|------|-------------------------------------|--------|--|--------------------|---|---|

|      |  |        |  |                    |   |  |
|------|--|--------|--|--------------------|---|--|
| NOS1 | human<br>neuronal<br>nitric<br>oxide<br>synthase | U17327 | AA239-988;<br>PDZ domain 1 (of 1)<br><br>IQPNVISVRLFKRKVGGLGFLVK<br>ERVSKPPVIISDLIRGAAEQSG<br>LIQAGDIILAVNGRPLVDLSYDS<br>ALEVLRGIASETHVVLILRGPEF<br>IVTD (SEQ ID NO:305) | Bam HI /<br>Eco RI | 155NOF<br><br>5'-<br>AGCGGATCCA<br>GCCCAATGTC<br>ATTTC-3'<br>(SEQ ID<br>NO:348) | 156NOR<br><br>5'-<br>GAAGAATTCAG<br>GGCCCCCTCAGA<br>ATG-3'<br>(SEQ ID<br>NO:349) |
|      |  |        |  |                    | N711-733  | N994-970   |

|     |                 |        |  |                    |  |   |
|-----|-----------------|--------|--|--------------------|--|---|
| AF6 | af-6<br>protein | U02478 | AA985-1077;<br>PDZ domain 1 (of 1)<br><br>LRKEPEIITVTLKKQNGMGLSIV<br>AAKGAGQDKLGIYVKSVMKGGAA<br>DVDGRLLAAGDQLLSVDGRSLVGL<br>SQERAAELMTRTSSVVTLEVAKQ<br>GEFIVTD (SEQ ID NO:306) | Bam HI /<br>Eco RI | 66AFF<br><br>5'-<br>TCGGATCCTG<br>AGGAAAGAAC<br>CTGAA-3'<br>(SEQ ID<br>NO:350) | 67AFR<br><br>5'-<br>TAGAATTCACC<br>CTGCTTTGCTA<br>CTTC-3'<br>(SEQ ID<br>NO:351) |
|     |                 |        |  |                    | N2946-2970   | N3239-3214  |

|        |                                   |        |   |                    |  |   |
|--------|-----------------------------------|--------|---|--------------------|--|---|
| PTN-4  | protein-tyrosine phosphatase meg1 | M68941 | AA774-862;<br>PDZ domain 1 (of 1)<br><br>LIRMKPDENGRFGNVKGYDQK<br>MPVIVSRVAPGTPADLCVPRLNE<br>GDQVVLINGRDIAETHDQVVLF<br>IKASCERHSGELMLLVPRPNAEFI<br>VTD (SEQ ID NO:307)  | Bam HI /<br>Eco RI | 247PTF<br><br>5'-<br>ATCGGATCCT<br>AATCAGAAATG<br>AAACCTG-3'<br>(SEQ ID<br>NO:352) | 248PTR<br><br>5'-<br>ATCGAATTCAG<br>CATTAGGTCGA<br>ACTAG-3'<br>(SEQ ID<br>NO:353) |
| prill6 | putative interleukin 16 precursor | S81601 | AA170-383;<br>PDZ domain 1-2 (of 2)<br><br>HVTILHKEEGAGLGFSLAGGADL<br>ENKVITVHRVFPNGLASQEGTIQ<br>KNEVLSINGKSLKGTTHHDALA<br>ILRQAREPRQAVIVTRKLTPEAM<br>PDLNSSTDASAASASDVSVES<br>TAEATVCTVTLEKMSAGLGSLE<br>GKGSLHGDKPLTINRIFKGAAS<br>EQSETVQPGDEILQLGGTAMQGL<br>TRFEAWNIIKALPDGPVTIVIRR<br>KSLQSKFEFIVTD (SEQ ID<br>NO:308) | Bam HI /<br>Eco RI | 75PRF<br><br>5'-<br>ACGGGATCCA<br>TGTCACCATC<br>TTACAC-3'<br>(SEQ ID<br>NO:354)    | 76PRR<br><br>5'-<br>GTGAATTCCTT<br>GGACTGGAGGC<br>TTTTTC-3'<br>(SEQ ID<br>NO:355) |
|        |                                   |        |   |                    | N2312-2338   | N2595-2569  |
|        |                                   |        |   |                    | N503-528   | N1157-1129  |

|         |  |          |   |                    |  |  |
|---------|--|----------|---|--------------------|--|--|
| 41.8 kD | hypothetical 41.8 kD protein               | AF007156 | AA4-85;<br>PDZ domain 1 (of 1)<br><br>RDSGAMLGKVVGGKMTESGRLC<br>AFITKVKKGLADTVGHLRPGDE<br>VLEWNGRLLQGATFEEVYNIILE<br>SKPEPQVELVVSRAVSS (SEQ<br>ID NO:309)                         | Bam HI /<br>Eco RI | 145HF<br><br>5' -<br>GTGGGATCCG<br>AGATTCAAGGA<br>GCAATGC-3'<br>(SEQ ID<br>NO:356) | 146HR<br><br>5' -<br>CTGGAATTTCGC<br>CTTGAAACTAC<br>AAGTTC-3'<br>(SEQ ID<br>NO:357)  |
| K559    | KIAA0559                                   | AB011131 | AA766-870;<br>PDZ1 (of 1)<br><br>HYIFPHARIKITRDSKDHTVSGN<br>GLGIRIVGGKEIPGHSGEIGAYI<br>AKILPGGSAEQTGKLMQGMQVLE<br>WNGIPLTSKTYEEVQSIISQQSG<br>EAEICVRLDLNMLSNSS (SEQ<br>ID NO:310) | Bam HI /<br>Eco RI | 130KIF<br><br>5' -<br>AAAGGATCCA<br>CTACATCTTT<br>CCTCAGC-3'<br>(SEQ ID<br>NO:358) | 131KIR<br><br>5' -<br>TCACAATTGGA<br>TAGCATATTGA<br>GGTCCAG-3'<br>(SEQ ID<br>NO:359) |
| RGS12   | human regulator of G-protein signalling 12 | AF035152 | AA35-103;<br>PDZ domain 1 (of 1)<br><br>PPPRVRSVEVARGAGYGFTLSG<br>QAPCVLSCVMRGSFADPFGVLRAG<br>DQILAVNEINVKKASHEDVVKLI<br>GNSS (SEQ ID NO:311)                                     | Bam HI /<br>Eco RI | 64RGF<br><br>5' -<br>TGGGATCCCG<br>CCCCCAAGGG<br>TGGGAG-3'<br>(SEQ ID<br>NO:360)   | 65RGR<br><br>5' -<br>AGGAATTCCCA<br>ATTAATTTCAC<br>TAC-3'<br>(SEQ ID<br>NO:361)      |

|      |          |          |  |                    |   |   |
|------|----------|----------|--|--------------------|---|---|
| K316 | KIAA0316 | AB002314 | AA197-284;<br>PDZ domain 1 (of 1)<br><br>PPAPRKVEMRRDPVLGFGFVAGS<br>EKPVVVRSVTPGGPSEGKLIPGD<br>QIVMINDEPVSAAPRERVIDLVR<br>SCKESILLTVIQYPSPKRNSS<br>(SEQ ID NO:312) | Bam HI /<br>Eco RI | 158KIF<br><br>5' -<br>AAAGGATCCC<br>TCCGGCTCCT<br>CGGAAG-3'<br>(SEQ ID<br>NO:362)<br><br>N586-611 | 159KIR<br><br>5' -<br>TTAGAATTCTG<br>ATTGGGAGAA<br>GGGTAAG-3'<br>(SEQ ID<br>NO:363)<br>N866-839 |
|------|----------|----------|--|--------------------|---|---|

|      |   |          |  |                    |   |  |
|------|---|----------|--|--------------------|---|--|
| DVL1 | human<br>dishevelled<br>segment<br>polarity<br>protein<br>homolog | AF006011 | AA248-340;<br>PDZ domain 1 (of 1)<br><br>QSTVLNIVTVTLNMERHHFLGIS<br>IVGQSNDRGDGGIYIGSIMKGA<br>VAADGRIEPGDMLLQVNDVNFEN<br>MSNDDAVRVLREIVSQTGPISLT<br>VAKCWEFIVTD (SEQ ID<br>NO:313) | Bam HI /<br>Eco RI | 1 <sup>st</sup> PCR:<br>55DVISF<br><br>5' -<br>TCATCCAGAC<br>TCATCCGGAA<br>G-3' (SEQ ID<br>NO:364)<br>N652-673<br><br>2 <sup>nd</sup> PCR,<br>nested:<br>37DVF<br><br>5' -<br>TCGGATCCAA<br>ACGGTCACTC<br>TCAAC-3' (SEQ ID<br>NO:366)<br>N723-747 | 1st PCR:<br>56DVISR<br><br>5' -<br>GCTCATGTCAC<br>TCTTCACCG-<br>3' (SEQ ID<br>NO:365)<br>N1195-1174<br><br>2 <sup>nd</sup> PCR,<br>nested:<br>38DVR<br><br>5' -<br>TCGGAATTCCC<br>AGCACTTGGCT<br>ACAG-3' (SEQ ID<br>NO:367)<br>N1029-N1004 |
|------|---|----------|--|--------------------|---|--|



|       |   |               |  |                    |  |  |
|-------|---|---------------|--|--------------------|--|--|
| TAX40 | human tax<br>interaction<br>protein 40                                | AF028827      | AA35-137;<br>PDZ domain 1 (of 1)<br><br>LLPETHRRVRLHKHGS DRPLGFY<br>IRDGMSVRVAPQGLERVP GIFIS<br>RLVRGG LAESTGLLAVSDEILEV<br>NGIEVAGKTLDQVTDMMVANS HN<br>LIVTVK PANQANSS (SEQ ID<br>NO:314) | Bam HI /<br>Eco RI | 136TF<br><br>5' -<br>ACGGGATCCT<br>ACTGCCTGAG<br>ACCCACC-3'<br>(SEQ ID<br>NO:368)<br><br>N97-123 | 137TR<br><br>5' -<br>ACGGAATCCG<br>CTGCTTGGCGG<br>GCTTGAC-3'<br>(SEQ ID<br>NO:369)<br>N421-393 |
| TIAM1 | T- lymphoma<br>invasion<br>and<br>metastasis<br>inducing<br>protein 1 | NM_<br>003253 | AA1001-1088;<br>PDZ 1 (of 1)<br><br>HSIHIEKSDTAADTYGFSLS SVE<br>EDGIRRLYVNSVKETGLASKKGL<br>KAGDEILEINNRAADALNSSMLK<br>DFLSQPSLGLLVRTYPELEEFIV<br>TD (SEQ ID NO:315)                        | Bam HI /<br>Eco RI | 39TF<br><br>5' -<br>TCGGATCCAC<br>AGCATCCACA<br>TTGAG-3'<br>(SEQ ID<br>NO:370)<br><br>N2995-3019 | 40TR<br><br>5' -<br>TCGGAATTCCT<br>CCAGCTCGGGG<br>T-3'<br>(SEQ ID<br>NO:371)<br><br>N3275-3253 |

|       |                   |        |  |                    |  |  |
|-------|-------------------|--------|--|--------------------|--|--|
| MINT1 | human X11 protein | L04953 | AA717-894;<br>PDZ domains 1-2 (of 2)<br><br>SENCKDVFIKQKGEILGVVIVE<br>SGWGSILPTVILANMMHGGPAEK<br>SGKLNIGDQIMSLVGLPL<br>STCQSIKGLNQSRVKLNIVRC<br>PPVTTLIRRPDLRYQLGFSVQN<br>GIICSLMRGGIAERGGVRVGHRI<br>IEINGQSVVATPHEKIVHILSNA<br>VGEIHMKTMPAAMYRLLNSS<br>( <u>SEQ ID NO:316</u> ) | Eco RI /<br>Eco RI | 34MIF<br><br>5' -<br>CGGAATTCGG<br>AAACTGTAA<br>AGATG-3'<br>( <u>SEQ ID NO:372</u> )<br><br>N2149-2167 | 20MR<br><br>5' -<br>TCGGAATTCAG<br>CAGCCTGTACA<br>TCG-3'<br>( <u>SEQ ID NO:373</u> )<br><br>N2690-2666 |
|-------|-------------------|--------|--|--------------------|--|--|

|      |          |          |   |                    |   |  |
|------|----------|----------|---|--------------------|---|--|
| K303 | KIAA0303 | Ab002301 | AA652-742;<br>PDZ domain 1 (of 1)<br><br>PHQPIVIHSSGKNYGFTIRAIRV<br>YVGSDIYTVHHIVMNVEEGSPA<br>CQAGLKAGDLITHINGEPVHGLV<br>HTEVIELLLKSGNKVSITTPFE<br>FIVTD ( <u>SEQ ID NO:317</u> ) | Bam HI /<br>Eco RI | 152KIF<br><br>5' -<br>CTGGGATCCC<br>ACATCAGCCG<br>ATTGTA-3'<br>( <u>SEQ ID NO:374</u> )<br><br>N1948-1976 | 153KIR<br><br>5' -<br>TGTGAATTCAA<br>ATGGGGTAGTA<br>GTGATTG-3'<br>( <u>SEQ ID NO:375</u> )<br><br>N2237-2209 |
|------|----------|----------|---|--------------------|---|--|

|     |                              |         |  |                    |   |  |
|-----|------------------------------|---------|--|--------------------|---|--|
| CBP | Cytohesin binding protein HE | AF68836 | AA85-176;<br>PDZ domain 1 (of 1)<br><br>QRKLVVEKQDNETFGFEIQSYR<br>PQNQNACSEMFTLICKIQEDSP<br>AHCAGLQAGDVLANINGVSTEGF<br>TYKQVVDLIRSSGNLLTITLNG<br>NSS (SEQ ID NO:318) | Bam HI /<br>Eco RI | 235CYF<br><br>5' -<br>CCTGGATCCA<br>AAGAAAGCTT<br>GTTACTGTG-<br>3' (SEQ ID<br>NO:376)<br>N246-274 | 236CYR<br><br>5' -<br>TCAGAAATTCCA<br>TTAAGAGTCTC<br>TATC-3'<br>(SEQ ID<br>NO:377)<br>N535-510 |
|-----|------------------------------|---------|--|--------------------|---|--|

|       |             |          |  |                    |  |  |
|-------|-------------|----------|--|--------------------|--|--|
| MINT3 | human MINT3 | AF029110 | AA11-52;<br>PDZ domain 1 (of 1)<br><br>PVTTAIIHRPHAREQLGFCVEDG<br>IVRRPLAPGWGGRAALSTEFIV<br>TD (SEQ ID NO:319) | Bam HI /<br>Eco RI | 188MF<br><br>5' -<br>ACTGGATCCC<br>CGTCACCACC<br>GCCATCATC-<br>3' (SEQ ID<br>NO:378)<br>N23-51 | 189MR<br><br>5' -<br>CTCGAATTCCG<br>TGCTCAGGGCC<br>GCCCTA-3'<br>(SEQ ID<br>NO:379)<br>N165-138 |
|-------|-------------|----------|--|--------------------|--|--|

|      |                                 |          |   |                    |  |  |
|------|---------------------------------|----------|---|--------------------|--|--|
| TAX2 | human tax interaction protein 2 | AF028824 | AA54-140;<br>PDZ domain 1 (of 1)<br><br>RKEVEVFKSEDALGLTITDNGAG<br>YAFIKRIKEGSVIDHIHLISVGD<br>MIEAINGQSLLGCRHYEVARLLK<br>ELPRGRTFTLKLTEPRKEFIVTD<br>(SEQ ID NO:320) | Bam HI /<br>Eco RI | 197 TF<br><br>5' -<br>AGGGGATCCG<br>CAAGGAGGTG<br>GAGGTGTTTC-<br>3' (SEQ ID<br>NO:380) | 198 TR<br><br>5' -<br>TGTGGAATTCC<br>TTGCGAGGCTC<br>CGTGAGC-3'<br>(SEQ ID<br>NO:381)<br>N429-401 |
|------|---------------------------------|----------|---|--------------------|--|--|

|      |          |          |  |                    |  |  |
|------|----------|----------|--|--------------------|--|--|
| K561 | KIAA0561 | AB011133 | AA948-1038;<br>PDZ domain 1 (of 1)<br><br>PPSLSTALARSTASACGRSASTW<br>VIATSTLCTTSSGVWRTEAPRR<br>RACGLGTSSPTSTGSQCWGWCTW<br>TSWSCCZRAATRYPCGPQPWRIH<br>RD ( <u>SEQ ID NO:321</u> ) | Bam HI /<br>Eco RI | N154-182<br>161KIF<br><br>5'-<br>CCTGGATCCC<br>CCCATCGTTA<br>TCCACAGC-<br>3'<br>( <u>SEQ ID<br/>NO:382</u> )<br>N2836-2863 | 162KIR<br><br>5'-<br>GAGGAATTCTC<br>CAGGGCTGTGG<br>TCCG-3'<br>( <u>SEQ ID<br/>NO:383</u> )<br>N3120-3095 |
|------|----------|----------|--|--------------------|--|--|

and Eco RI, Bam HI and Mfe I, or Eco RI only, Sma I only, or BamHI only (see **TABLE 3**). When more than one PDZ domain was cloned, the DNA portion cloned represents the PDZ domains and the cDNA portion located between individual domains. Precise locations of cloned fragments used in the assays are indicated in **TABLE 3**. DNA linker sequences between the GST portion and the PDZ domain containing DNA portion vary slightly, dependent on which of the above described cloning sites and approaches were used. As a consequence, the amino acid sequence of the GST-PDZ fusion protein varies in the linker region between GST and PDZ domain. Protein linkers sequences corresponding to different cloning sites/approaches are shown below. Linker sequences (vector DNA encoded) are bold, PDZ domain containing gene derived sequences are in italics.

- 1) **GST—BamHI/BamHI—** *PDZ domain insert*  
**Gly--Ile—***PDZ domain insert*
- 2) **GST—BamHI/BglII—** *PDZ domain insert*  
**Gly—Ile—***PDZ domain insert*
- 3) **GST—EcoRI/EcoI—** *PDZ domain insert*  
**Gly—Ile—Pro—Gly--Asn—***PDZ domain insert* (SEQ ID NO:258)
- 4) **GST--SmaI/SmaI—** *PDZ domain insert*  
**Gly—Ile—Pro—***PDZ domain insert*

Paragraph (TABLE 4) beginning at line 1 of page 60 has been amended as follows (see attached sheets).

Paragraph beginning at line 4 of page 66 has been amended as follows:

Other investigators have reported certain PL motifs important in PDZ binding, e.g., the C-terminal motifs S/T-X-V/I/L (for DLG1) and Y/F-Y/F-I/L/F for MPP1 (see, Doyle et al., 1996, Cell 85, 1067; Songyang et al., 1997, Science 275, 73). However, the reported motifs are not sufficiently specific (i.e. a large number of proteins meet these criteria yet are not necessarily actual PDZ ligands) and cover only a small number of PDZ proteins (approximately 10). The PRISM MATRIX can be used to determine ligand specificity and to deduce ligand binding motifs for any PDZ protein because it can precisely determine

| <b>Table 4: PL Peptides</b>  |                     |                       |                       |                   |
|--|---------------------|-----------------------|-----------------------|-------------------|
| <b>CODE</b>  | <b>PROTEIN NAME</b> | <b>GENBANK ACCESS</b> | <b>SEQUENCE</b>       | <b>SEQ ID NO:</b> |
| AA1L   | Clasp-1             |                       | ISKATPALPTVSISSSAEV   | <u>177</u>        |
| AA2L   | Clasp-2             |                       | ISGTPSTMTVMHGMTSSSSV  | <u>178</u>        |
| AA3L   | Clasp-4             |                       | CAISGTSSDRGYGSPRYAEV  | <u>179</u>        |
| AA4L   | CD3n                | M33158                | SVFSIPTLWSPWPPSSSSQL  | <u>180</u>        |
| AA5L-M*  | CD4                 | M12807                | SEKTSQSPHRFQKTCSPI    | <u>181</u>        |
| AA6L   | CD6                 | X60992                | SPQPDSTDNDYDDISAA     | <u>182</u>        |
| AA7L   | CD34                | M81104                | QATSRNGHSARQHVADTEL   | <u>183</u>        |
| AA9L   | CD44                | M69215                | QFMTADETRNLQNVDMKIGV  | <u>184</u>        |
| AA10L  | CD46 (Form 1)       | M58050                | KKGTYLTDETHREVKFTSL   | <u>185</u>        |
| AA11L  | CD49E ( 4 )         | X06256                | PYGTAMEKAQLKPPATSDA   | <u>186</u>        |
| AA12L  | CD49F               | X53586                | HKAEIHAQPSDKERLTSDA   | <u>187</u>        |
| AA13L  | CD95                | M67454                | KDITSDSENSNFRNEIQSLV  | <u>188</u>        |
| AA14L  | CD97                | X84700                | TSGTGHNQTRALRASESGI   | <u>189</u>        |
| AA15L  | CD98                | J02939                | ERLKLEPHEGLLLRFPYAA   | <u>190</u>        |
| AA16L  | CD105               | X72012                | STNHSIGSTQSTPCSTSSMA  | <u>191</u>        |
| AA17L  | VCAM1               | M73255                | ARKANMKGSYSLVEAQSKV   | <u>192</u>        |
| AA18L  | CD138               | J05392                | PKQANGGAYQKPTQEEFYA   | <u>193</u>        |
| AA19L  | CD148               | D37781                | ENLAPVTTFGKTINGYIA    | <u>194</u>        |
| AA20L  | CD166               | L38608                | DLGNMEENKKLEENNHKTEA  | <u>195</u>        |
| AA22L  | DNAM-1              | U56102                | TREDIYVNYPTFSRRPKTRV  | <u>196</u>        |
| AA23L-M*   | FasL                | U11821                | SSKSKSSEESQTFGLYKL    | <u>197</u>        |
| AA25L  | FceRIb              | D10583                | YSATYSELEDPGEMSPPIDL  | <u>198</u>        |
| AA28L  | CDW125 (IL5R)       | X62156                | EVICYIEKPGVETLEDV     | <u>199</u>        |
| AA29.1L  | CDW128A (IL8RA)     | M68932                | ARHRVTSYTSSSVNVSSNL   | <u>200</u>        |
| AA29.2L  | CDW128B (IL8RB)     | M73969                | KDSRPSFVGSSSGHTSTTL   | <u>201</u>        |
| AA30L  | LPAP                | X81422                | AWDDSARAAGGQGLHVTAL   | <u>202</u>        |
| AA33L  | KV1.3               | AAC31761              | TTNNNPNSAVNIKKIFTDV   | <u>203</u>        |
| AA34.2L  | NMDA                | NP000824              | LNSCSNRRVYKKMPSIESDV  | <u>204</u>        |
| AA37L  | Glycophorin C       | AAA52574              | QGDPALQDAGDSSRKEYFI   | <u>205</u>        |
| AA38L  | Neurexin            | AB011150              | SSAKSSNKNKNKDKEYV     | <u>206</u>        |
| AA39L  | Syndecan-2          | A33880                | GERKPSSAAYQKAPTKEFYA  | <u>207</u>        |
| AA40L  | DOCK2               | BAA13200              | LASKSAEEGKQIPDSLSTDL  | <u>208</u>        |
| AA41L  | CC CKR-1R           | L09230                | LERVSSTSPSTGEHELSTAGF | <u>209</u>        |
| AA42L  | CC CKR-2            | U03882                | GKGKSIGRAPEASLQDKEGA  | <u>210</u>        |
| AA43L  | CC CKR-3            | HSU28694              | LERTSSVSPSTAEPESLIVF  | <u>211</u>        |
| AA44L  | CC CKR-4            | X85740                | DTPSSSYTQSTMDHDLHDAL  | <u>212</u>        |
| AA45L  | BLR-1               | S56162                | PSWRRSSLSESENATSLTTF  | <u>213</u>        |
| AA47L  | CD83                | Z11697                | VTSPNKHGLVTPHKTEL     | <u>214</u>        |
| AA48L  | CD62E               | M30640                | SSSQSLES DGSYQKPSYIL  | <u>215</u>        |
| AA49L  | CD5                 | X04391                | SMQPDNSSDSYDLHGAQRL   | <u>216</u>        |
| AA55L  | CD148               | D37781                | TIYENLAPVTTFGKTIA     | <u>217</u>        |
| *The Sequence studied is mutated at positions >10 amino acids from C-terminus to increase water solubility and/or eliminate intramolecular disulfides. |                     |                       |                       |                   |

sequences of amino acids that do or do not result in specific PDZ binding. In addition, the assay has revealed a significant of new PDZ domain binding motifs (i.e. PL motifs): C-terminal sequence of CD6, ISAA (SEQ ID NO:14); C- terminal sequence of CD49E, TSDA (SEQ ID NO:24); C- terminal sequence of CD49F, TSDA (SEQ ID NO:24); C-terminal sequence of ~~CLASP-1~~ ~~Clasp-1~~, SAEV (SEQ ID NO:289); C- terminal sequence of CLASP-4, YAEV (SEQ ID NO:228); C- terminal sequence of CD44, KIGV (SEQ ID NO:104); C-terminal sequence of IL5R, DSVF (SEQ ID NO:94); and C-terminal sequence of BLR-1, LTTF (SEQ ID NO:253). Identification of these novel PL sequences allows the definition of novel PL motifs (See **TABLE 5A**, *infra*). The specificity with which these novel motifs are defined is enhanced by the fact that the MATRIX reports both positive results (i.e. PDZ-PL) combinations that result in specific binding interactions) and negative results (i.e. PDZ-PL combinations that do not result in specific binding). For example, the C-terminal sequence of CD6, SAA and the C-terminal sequence of CD49E, SDA bind to the PDZ-domain polypeptide 41.8 while the related C-terminal sequence of CD166, TEA and C- terminal sequence of CD148, YIA do not. This identifies the novel PL motif (Motif 1, *infra*) of polypeptides terminating in alanine with serine at the -2 position and excludes polypeptides with threonine and tyrosine at the -2 position. This motif is therefore more specific than most previously identified motifs. Other novel motifs are described in **TABLE 5A**.

Paragraph beginning at line 9 of page 106 has been amended as follows:

**FIGURES 3A-H** show the use of peptides to inhibit PL-PDZ interactions using the G assay described *supra*. In **FIGURE 3A and B**, the inhibition assays were carried out using GST fusion proteins containing PDZ domains from DLG1 or PSD95 (see *supra* and **TABLE 3**). Binding of biotinylated PL peptides for ~~CLASP-2~~ ~~Clasp-2~~, CD46, Fas, or KV1.3 (as listed in **TABLE 4**) was determined in the presence of various competitor peptides (at a concentration of 100 uM) or in the absence of a competitor (equalized as 100% binding). The competitor peptides were 8-mers peptides -having the sequence of C-terminus of ~~CLASP-2~~ ~~Clasp-2~~ (MTSSSSVV; SEQ ID NO:227), CD46 (REVKFTSL; SEQ ID NO:113), or Fas (TFFGLYKL; SEQ ID NO:83) (~~RNEIQSLV~~), a unlabeled 19-mer having the sequence of c-terminus of KV1.3 (i.e., non-biotinylated AA33L as listed in **TABLE 4** ~~TABLE 3~~), or a peptide having the sequence of residues 64-76 of hemoglobin (Vidal et al.,

1999, *J. Immunol.* 163, 4811), i.e., an unrelated competitor. The binding of biotinylated peptide (10 uM for Fas and KV1.3, 20 uM for CLASP-2 ~~Clasp-2~~ and CD46) to GST alone was subtracted from the binding to the fusion proteins to obtain the net signal for each experimental condition. This net signal was then normalized by dividing by the signal in the absence of competitor peptide and the data were plotted. Error bars indicated the standard deviation of duplicate measurements. Specific inhibition of CLASP-2 ~~Clasp-2~~ PL-DLG PDZ binding was observed with the CLASP-2 8-mer, the CD46 8-mer, the Fas 8-mer ~~FAS 8-mer~~, and the KV1.3 ~~KV13~~ peptide, but not in the absence of peptide or using an unrelated peptide.

Paragraph beginning at line 24 of page 106 has been amended as follows:

**FIGURES 3C-F** show similar assays using shorter peptides to inhibit (e.g., a 3-mer and a 5-mer). **FIGURES 3C-E** ~~Figures 3C-E~~ show binding of biotinylated PL peptides for CLASP-2 ~~Clasp-2~~, CD46, Fas, or KV1.3, at the indicated concentration (as listed in **TABLE 3**) to GST fusion proteins containing PDZ domains from NeDLG, DLG1, or PSD95 in the absence or presence of 1 mM 3-mer peptide having the sequence of the C-terminus of Clasp 2 (SVV) (TABLE 3) ~~(Table 3)~~. **FIGURE 3F** shows the effect on binding of a 5-mer CD49E peptide (ATSDA; SEQ ID NO:25) ~~(ATSDA)~~ to GST fusion proteins containing a PDZ domain from 41.8Kd.

Paragraph beginning at line 3 of page 109 has been amended as follows:

The C-terminal core sequence of CD49f is TSDA (SEQ ID NO:24) ~~(SEQ ID NO:29)~~. When naturally-occurring residues are added to the core sequence, LTSDA (SEQ ID NO:30), RLTSDA (SEQ ID NO:31), ERLTSDA (SEQ ID NO:32), and KERLTSDA (SEQ ID NO:33) may also be used to target a PDZ domain-containing protein in T cells.

Paragraph beginning at line 11 of page 109 has been amended as follows:

The C-terminal core sequence of CD83 is TELV (SEQ ID NO:248) ~~(SEQ ID NO:248)~~. When naturally-occurring residues are added to the core sequence, KTELV (SEQ



~~ID NO:249) (SEQ. ID. NO: 249)~~, HKTEL V (SEQ ID NO:250) (~~SEQ. ID. NO: 250~~),  
PHKTEL V (SEQ ID NO:251) (~~SEQ. ID. NO: 251~~), and TPHKTEL V (SEQ ID NO:252)  
(~~SEQ. ID. NO: 252~~) may also be used to target a PDZ domain-containing protein in T cells.

Paragraph beginning at line 21 of page 110 has been amended as follows:

The C-terminal core sequence of CLASP-1 is SAQV (SEQ ID NO:218) (~~SEQ. ID. NO: 218~~). When naturally-occurring residues are added to the core sequence, SSAQV (SEQ ID NO:219) (~~SEQ. ID. NO: 219~~), SSSAQV (SEQ ID NO:220) (~~SEQ. ID. NO: 220~~), ISSAQV (SEQ ID NO:221) (~~SEQ. ID. NO: 221~~), and SISSAQV (SEQ ID NO:222) (~~SEQ. ID. NO: 222~~) may also be used to target a PDZ domain-containing protein in T cells.

Paragraph beginning at line 25 of page 110 has been amended as follows:

The C-terminal core sequence of CLASP-2 is SSVV (SEQ ID NO:223) (~~SEQ. ID. NO: 223~~). When naturally-occurring residues are added to the core sequence, SSSVV (SEQ ID NO:224) (~~SEQ. ID. NO: 224~~), SSSSVV (SEQ ID NO:225) (~~SEQ. ID. NO: 225~~), TSSSVV (SEQ ID NO:226) (~~SEQ. ID. NO: 226~~), and MTSSSVV (SEQ ID NO:227) (~~SEQ. ID. NO: 227~~) may also be used to target a PDZ domain-containing protein in T cells.

Paragraph beginning at line 29 of page 110 has been amended as follows:

The C-terminal core sequence of CLASP-4 is YAEV (SEQ ID NO:228) (~~SEQ. ID. NO: 228~~). When naturally-occurring residues are added to the core sequence, RYAEV (SEQ ID NO:229) (~~SEQ. ID. NO: 229~~), PRYAEV (SEQ ID NO:230) (~~SEQ. ID. NO: 230~~), SPRYAEV (SEQ ID NO:231) (~~SEQ. ID. NO: 231~~), and GSPRYAEV (SEQ ID NO:232) (~~SEQ. ID. NO: 232~~) may also be used to target a PDZ domain-containing protein in T cells.

Paragraph beginning at line 33 of page 110 has been amended as follows:

The C-terminal core sequence of KV1.3 is FTDV (SEQ ID NO:238) (~~SEQ. ID. NO: 238~~). When naturally-occurring residues are added to the core sequence, IFTDV (SEQ ID NO:239) (~~SEQ. ID. NO: 239~~), KIFTDV (SEQ ID NO:240) (~~SEQ. ID. NO: 240~~), KKIFTDV (SEQ ID NO:241) (~~SEQ. ID. NO: 241~~), and IKKIFTDV (SEQ ID NO:242) (~~SEQ. ID. NO: 242~~) may also be used to target a PDZ domain-containing protein in T cells.

Paragraph beginning at line 3 of page 111 has been amended as follows:

The C-terminal core sequence of DOCK2 is STD L (SEQ ID NO:243) (~~SEQ. ID. NO: 243~~). When naturally-occurring residues are added to the core sequence, LSTD L (SEQ ID NO:244) (~~SEQ. ID. NO: 244~~), SLSTD L (SEQ ID NO:245) (~~SEQ. ID. NO: 245~~), DSLSTD L (SEQ ID NO:246) (~~SEQ. ID. NO: 246~~), and PDSLSTD L (SEQ ID NO:247) (~~SEQ. ID. NO: 247~~) may also be used to target a PDZ domain-containing protein in T cells.

Paragraph beginning at line 22 of page 111 has been amended as follows:

The C-terminal core sequence of Syndecan-2 is EFYA (SEQ ID NO:89) (~~SEQ. ID. NO: 258~~). When naturally-occurring residues are added to the core sequence, KEFYA (SEQ ID NO:259) (~~SEQ. ID. NO: 259~~), TKEFYA (SEQ ID NO:260) (~~SEQ. ID. NO: 260~~), PTKEFYA (SEQ ID NO:261) (~~SEQ. ID. NO: 261~~), and APTKEFYA (SEQ ID NO:262) (~~SEQ. ID. NO: 262~~) may also be used to target a PDZ domain-containing protein in B cells.

Paragraph beginning at line 26 of page 111 has been amended as follows:

The C-terminal core sequence of BLR-1 is LTTF (SEQ ID NO:253) (~~SEQ. ID. NO: 253~~). When naturally-occurring residues are added to the core sequence, SLTTF (SEQ ID NO:254) (~~SEQ. ID. NO: 254~~), TSLTTF (SEQ ID NO:255) (~~SEQ. ID. NO: 255~~), ATSLTTF (SEQ ID NO:256) (~~SEQ. ID. NO: 256~~), and NATSLTTF (SEQ ID NO:257) (~~SEQ. ID. NO: 257~~) may also be used to target a PDZ domain-containing protein in B cells.

Paragraph beginning at line 5 of page 114 has been amended as follows:

The C-terminal core sequence of CD105 is SSMA (SEQ ID NO:159). When naturally-occurring residues are added to the core sequence, TSSMA (SEQ ID NO:160), STSSMA (SEQ ID NO:161), CSTSSMA (SEQ ID NO:291) (~~SEQ ID NO:162~~) and PCSTSSMA (SEQ ID NO:162) (~~SEQ ID NO:162~~) may also be used to target a PDZ domain-containing protein in endothelial cells.

Paragraph beginning at line 17 of page 114 has been amended as follows:

The C-terminal core sequence of VCAM1 is KSKV (SEQ ID NO:163) (~~SEQ ID NO:233~~). When naturally-occurring residues are added to the core sequence, QKSKV (SEQ ID NO:164) (~~SEQ ID NO:234~~), AQKSKV (SEQ ID NO:165) (~~SEQ ID NO:235~~), EAQKSKV (SEQ ID NO:166) (~~SEQ ID NO:236~~), and VEAQKSKV (SEQ ID NO:167) (~~SEQ ID NO:237~~) may also be used to target a PDZ domain-containing protein in endothelial cells.

Paragraph beginning at line 23 of page 114 has been amended as follows:

FcεRIβ, CDw125, CDw128 and IL-8RB are transmembrane receptors expressed by mast cells, basophils and eosinophils. These receptors play a role in the activation of these cells to result in degranulation and histamine release in allergic reactions. The C-terminal core sequence of FcεRIβ is PIDL (SEQ ID NO:129) (~~SEQ ID NO:4~~). When naturally-occurring residues are added to the core sequence, PPIDL (SEQ ID NO:130) (~~SEQ ID NO:5~~), SPPIDL (SEQ ID NO:131) (~~SEQ ID NO:6~~), MSPPIDL (SEQ ID NO:132) (~~SEQ ID NO:7~~) and EMSPPIDL (SEQ ID NO:133) (~~SEQ ID NO:8~~) may also be used to target a PDZ domain-containing protein in mast cells. In addition, the residue E may be substituted with G to increase its binding affinity.

Paragraph beginning at line 31 of page 114 has been amended as follows:

The C-terminal core sequence of CDw125 is DSVF (SEQ ID NO:94) (~~SEQ ID NO:9~~). When naturally-occurring residues are added to the core sequence, EDSVF (SEQ ID NO:95) (~~SEQ ID NO:10~~), LEDSVF (SEQ ID NO:96) (~~SEQ ID NO:11~~), TLEDSVF (SEQ ID NO:97) (~~SEQ ID NO:12~~), and ETLEDSVF (SEQ ID NO:98) (~~SEQ ID NO:13~~) may also be used to target a PDZ domain-containing protein in mast cells.

Paragraph beginning at line 1 of page 115 has been amended as follows:

The C-terminal core sequence of CDw128 is SSNL (SEQ ID NO:69) (~~SEQ ID NO:14~~). When naturally-occurring residues are added to the core sequence, VSSNL (SEQ ID NO:70) (~~SEQ ID NO:15~~), NVSSNL (SEQ ID NO:71) (~~SEQ ID NO:16~~), VNVSSNL (SEQ ID NO:72) (~~SEQ ID NO:17~~), and SVNSSNL (SEQ ID NO:73) (~~SEQ ID NO:18~~) may also be used to target a PDZ domain-containing protein in mast cells.

Paragraph beginning at line 5 of page 115 has been amended as follows:

The C-terminal core sequence of IL-8RB is STTL (SEQ ID NO:233) (~~SEQ ID NO:19~~). When naturally-occurring residues are added to the core sequence TSTTL (SEQ ID NO:234) (~~SEQ ID NO:20~~), HTSTTL (SEQ ID NO:235) (~~SEQ ID NO:21~~), GHTSTTL (SEQ ID NO:236) (~~SEQ ID NO:22~~) and SGHTSTTL (SEQ ID NO:237) (~~SEQ ID NO:23~~) may also be used to target a PDZ domain-containing protein in mast cells.

Paragraph beginning at line 10 of page 115 has been amended as follows:

The C-terminal core sequence of NMDA is ESDV (SEQ ID NO:263) (~~SEQ ID NO:263~~). When naturally-occurring residues are added to the core sequence, IESDV (SEQ ID NO:264) (~~SEQ ID NO:264~~), SIESDV (SEQ ID NO:265) (~~SEQ ID NO:265~~), PSIESDV (SEQ ID NO:266) (~~SEQ ID NO:266~~), and MPSIESDV (SEQ ID NO:267) (~~SEQ ID NO:267~~) may also be used to target a PDZ domain-containing protein in neuronal cells.

Paragraph beginning at line 14 of page 115 has been amended as follows:

The C-terminal core sequence of neurexin is EYYV (SEQ ID NO:268) (~~SEQ ID NO: 268~~). When naturally-occurring residues are added to the core sequence, KEYYV (SEQ ID NO:269) (~~SEQ ID NO: 269~~), DKEYYV (SEQ ID NO:270) (~~SEQ ID NO: 270~~), KDKEYYV (SEQ ID NO:271) (~~SEQ ID NO: 271~~), and NKDKEYYV (SEQ ID NO:272) (~~SEQ ID NO: 272~~) may also be used to target a PDZ domain-containing protein in neuronal cells.

Paragraph beginning at line 19 of page 115 has been amended as follows:

The C-terminal core sequence of Glycophorin C is EYFI (SEQ ID NO:273) (~~SEQ ID NO: 273~~). When naturally-occurring residues are added to the core sequence, KEYFI (SEQ ID NO:274) (~~SEQ ID NO: 274~~), RKEYFI (SEQ ID NO:275) (~~SEQ ID NO: 275~~), SRKEYFI (SEQ ID NO:276) (~~SEQ ID NO: 276~~), and SSRKEYFI (SEQ ID NO:277) (~~SEQ ID NO: 277~~) may also be used to target a PDZ domain-containing protein.

Paragraph beginning at line 23 of page 115 has been amended as follows:

The C-terminal core sequence of CD148 is KTIA (SEQ ID NO:278) (~~SEQ ID NO: 278~~). When naturally-occurring residues are added to the core sequence, GKTIA (SEQ ID NO:279) (~~SEQ ID NO: 279~~), FGKTIA (SEQ ID NO:280) (~~SEQ ID NO: 280~~), TFGKTIA (SEQ ID NO:281) (~~SEQ ID NO: 281~~), and TTFGKTIA (SEQ ID NO:282) (~~SEQ ID NO: 282~~) may also be used to target a PDZ domain-containing protein in epithelial or myeloid cells.

Paragraph beginning at line 9 of page 138 has been amended as follows:

All peptides were chemically synthesized by standard procedures. The Tat-CD3 carboxyl terminus fusion peptide, (GYGRKKRRQRRRGPPSSSSGL, SEQ ID

NO:174); Tat-CLASP1 carboxyl terminus fusion peptide, (GYGRKKRRQRRRGSISSSAEV, SEQ ID NO:175); Tat-CLASP2 carboxyl terminus fusion peptide, (GYGRKKRRQRRRGMTSSSSVV, SEQ ID NO:176); and Tat peptide, (GYGRKKRRQRRRG, ~~SEQ ID NO:289~~ ~~SEQ ID NO:—~~); were dissolved at 1 mM in PBS, pH 7, or dH<sub>2</sub>O. Stock MBPac1-16 peptide, (AcASQKRPSQRHGSKYLA; SEQ ID NO:290), was dissolved at 5 mM. All peptides were aliquoted and stored at -80°C until tested.

Paragraph beginning at line 24 of page 140 has been amended as follows:

To detect such inhibition, it was necessary to synthesize an analogue of the CLASP2peptide AA2L that (1) retained similar DLG1 binding properties and (2) would not itself generate a signal in the assay selected to measure inhibition. Because most molecular interactions between PDZ proteins and their ligands involve only the C-terminal 6 amino acids of the ligand, an eight amino acid variant of the CLASP-2 peptide, MTSSSSVV (SEQ ID NO:227), was anticipated to retain similar DLG1 binding properties as the 20 amino acid AA2L CLASP-2 peptide. This eight amino acid CLASP-2 peptide (lacking a functional label) was therefore synthesized and purified by standard techniques as described *supra*. When 100 uM of the (functionally unlabeled) eight amino acid CLASP-2 peptide and 20 uM of the biotin-labeled AA2L CLASP-2 peptide were added simultaneously to DLG1 in a variant of the “G” assay (described *supra*), the binding of the labeled AA2L CLASP-2 peptide was, as predicted, inhibited by greater than 50% (**FIGURE 3A**). An analogous experiment in which the labeled AA2L CLASP-2 peptide was replaced with another labeled DLG1 ligand, labeled AAI3L Fas peptide demonstrated similar inhibition by the eight amino acid CLASP-2 peptide (**FIGURE 3A**). Thus, an effective inhibitor of DLG1-ligand binding (i.e. the eight amino acid CLASP-2 peptide MTSSSSVV; SEQ ID NO:227) with a known potency range (order of magnitude 21 uM) was designed based on knowledge of the affinity, 21 uM, with which a particular labeled ligand, the CLASP-2 peptide AA2L; bound to DLG1.